In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: February 9, 2016

* * * * * * * * * * * * * *	PUBLISHED DECISION
LESLIE LORD *and* RANDALL MAGNUSKI, *legal representatives of a deceased minor child*, C.L.,	No. 12-255V
Petitioners,	Chief Special Master Dorsey
v.	Denial of Entitlement; Hepatitis B (Hep B) Vaccine; Inactivated Polio (IPV) Vaccine;
SECRETARY OF HEALTH AND HUMAN SERVICES,	DTaP Vaccine; Haemophilus Influenza (Hib) Vaccine; Pneumococcal Conjugate (PCV) Vaccine; Rotavirus
Respondent.	Vaccine; Sudden Infant Death Syndrome (SIDS)
* * * * * * * * * * * * * *	

Ronald C. Homer, Conway, Homer & Chin-Caplan, P.C., Boston, MA, for petitioners.
Jennifer L. Reynaud, United States Department of Justice, Washington, DC, for respondent.

DECISION[1]

Leslie Lord and Randall Magnuski ("petitioners") filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"),[2] 42 U.S.C. § 300aa-10 et seq. (2012), as the representatives of the estate of their deceased minor child, C.L. Petitioners alleged that C.L. died on May 13, 2011, as a result of receiving the hepatitis B ("Hep B"); Diphtheria-Tetanus-acellular-Pertussis ("DTaP"), inactivated polio ("IPV"), haemophilus influenza ("Hib"); Pneumococcal Conjugate ("PCV"); and Rotavirus vaccinations on May 11, 2011. See Petition, filed Apr. 18, 2012, at 1 n.1, ¶ 8; Amended Petition, filed May 23, 2013, at 1. Respondent recommended against awarding compensation to petitioners. See Respondent's Response ("Resp. Res."), filed Aug. 8, 2013, at 1.

[1] Because this decision contains a reasoned explanation for the undersigned's action in this case, the undersigned intends to post this ruling on the website of the United States Court of Federal Claims, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012)(Federal Management and Promotion of Electronic Government Services). As provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b).

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

After carefully analyzing and weighing all of the evidence and testimony presented in this case in accordance with the applicable legal standards, the undersigned finds that petitioners have not met their legal burden. Petitioners have failed to provide preponderant evidence that the vaccinations C.L. received on May 11, 2011, caused his death. Accordingly, petitioners are not entitled to compensation.

The undersigned notes that her decision in this case is consistent with those in other similar SIDS cases heard by special masters in the Vaccine Program (and upheld on review), in which petitioners have been denied entitlement because of the lack of sufficient proof of causation. See, e.g., Doe/11 v. Sec'y of Health & Human Servs., 601 F.3d 1349 (Fed. Cir. 2010) (upholding Special Master Campbell-Smith's decision that a death labeled "SIDS" was not caused by a hepatitis B vaccine); Waterman v. Sec'y of Health & Human Servs., No. 13-960V, 2015 WL 4481244 (Fed. Cl. Spec. MsTr. at June 30, 2015) (aff'd 123 Fed. Cl. 564 (Fed. Cl. 2015) (Chief Judge Campbell-Smith)) (Special Master Hamilton-Fieldman denied entitlement in a SIDS case finding that petitioners did not prove that their child suffered an encephalopathy prior to his death); Sanchez v. Sec'y of Health & Human Servs., No. 11-651V, 2013 WL 4476750 (Fed. Cl. Spec. MsTr. at July 26, 2013) (Special Master Millman found that petitioner failed to prove that vaccinations caused SIDS death); Bigbee v. Sec'y of Health & Human Servs., No. 06-663V, 2012 WL 1237759 (Fed. Cl. Spec. MsTr. at Mar. 22, 2012) (Special Master Golkiewicz held that petitioners failed to produce preponderant evidence that the vaccines caused the child's death); Nordwall v. Sec'y of Health & Human Servs., No. 05-0123V, 2008 WL 857661 (Fed. Cl. Spec. MsTr. at Feb. 19, 2008) (Special Master Moran held that a SIDS death was not due to a vaccine but rather "positional asphyxia") (mot. for review denied, 83 Fed. Cl. 477 (Fed. Cl. 2008)); and Heller v. Sec'y of Health & Human Servs., No. 96-797V, 1998 WL 408612 (Fed. Cl. Spec. MsTr. at June 22, 1998) (Special Master Millman found that studies did not show a causal link and that petitioner failed to demonstrate a causal relationship between DPT vaccine and SIDS).

I. BACKGROUND

A. Procedural History

On April 18, 2012, petitioners filed a petition for compensation on behalf of their deceased minor son, C.L., pursuant to the Vaccine Act. On May 23, 2013, petitioners filed an amended petition alleging that "as a result of receiving [the] vaccinations on May 11, 2011, [C.L.] died on May 13, 2011." Amended Petition at 1.

Petitioners filed the expert report of Dr. Douglas C. Miller, a neuropathologist, on February 8, 2013, along with the medical literature referenced in Dr. Miller's report. See Pet. Exs. 22-46. In a status report filed March 28, 2013, respondent noted that petitioners had filed expert reports espousing the same theory of causation, with the same literature, and from the same expert, as petitioners in Cozart, 00-590V, and Sexton, 99-453V. Resp. Status Rep., filed March 28, 2013. Because of this overlap, respondent requested that common testimony be taken for all three cases at one hearing. Id. Petitioners, however, opposed such a consolidation. Pet. Status Rep., file June 14, 2013, at 2. After a status conference on July 9, 2013, the undersigned ordered the parties to proceed with proposing dates for a hearing in this case only, and the cases were not consolidated. See Order, filed July 9, 2013.

Respondent filed the expert report of Dr. Hart Lidov, a neuropathologist, on May 28, 2013, followed by the medical literature referenced in his report on June 4, 2013. See Resp. Ex. A.[3] Respondent also filed an expert report from Dr. Christine McCusker, an immunologist, on August 8, 2013, followed by the medical literature referenced in her report on August 9, 2013. Resp. Ex. C. On August 8, 2013, respondent filed her Rule 4(c) report advising against compensation.

Petitioners filed an expert report from Dr. James Oleske, an immunologist, on December 11, 2013, along with the medical literature referenced in his report. Pet. Ex. 50. Respondent filed a supplemental expert report from Dr. Christine McCusker on February 10, 2014. See Resp. Ex. E. Respondent filed two additional medical articles on July 17, 2015. Resp. Exs. F, G.

At numerous stages of this case, the undersigned encouraged the parties to pursue the possibility of an informal resolution, and/or to consider mediation. See, e.g. Order, filed July 9, 2013; Order, filed October 29, 2013; Order, filed June 26, 2015. The parties made several attempts but were ultimately unable to resolve the case informally before hearing. See, e.g. Joint Status Rep., filed March 28, 2014; Joint Status Rep., filed July 9, 2015.

An entitlement hearing was held on Wednesday, July 29, and Thursday, July 30, 2015, in Washington, D.C. Dr. Miller testified on behalf of petitioners, and Drs. McCusker and Lidov testified on behalf of respondent. Dr. Oleske did not testify. After the hearing, the parties filed additional medical literature referenced by their experts during the hearing. See Pet. Exs. 57-61; Resp. Exs. F-H.[4] Petitioners filed a status report indicating that they did not intend to present additional expert testimony from Dr. Oleske. Pet. Status Rep., filed Aug. 31, 2015. Petitioners filed their post-hearing brief on October 26, 2015, and respondent filed her post-hearing brief on December 2, 2015.

This matter is now ripe for adjudication.

B. Summary of Relevant Facts

C.L. was born prematurely on November 6, 2010, at just under thirty-six weeks gestation. Pet. Ex. 1; Pet. Ex. 2 at 4. A few hours after birth, C.L. became hypothermic and was noted to show decreased peripheral blood oxygen content ("desaturation"). See Pet. Ex. 22 at 4. However, he was subsequently observed to be growing and developing normally at his one, two, and four-month well-baby checkups. Pet. Ex. 4 at 4, 6, 13. At his one month checkup, the pediatrician noted that his father smoked outside of the family home. Id. at 3. In addition, the pediatrician noted that C.L. was "sleeping in rocker with pillow underneath and blanket tucked tightly in rocker. . . aware of increased risk of SIDS with pillows and blanket." Id. On physical exam at his two-month visit, the pediatrician noted that C.L. was "not yet fixing and following" and had a "dysconjugate gaze." Id. at 6. At his four month checkup, however, he was noted to fix and follow. Id. at 12. C.L. received

[3] The medical records filed by petitioner included handwritten pagination, and citations to medical records in this decision are to the handwritten page number. The majority of the expert reports and medical literature filed by both parties, however, was not individually paginated, therefore citations in this decision are to the case management electronic case filing system (CM/ECF) pdf page number.

[4] Respondent's exhibits appear to be mislabeled, as she had already filed exhibits labeled F and G on July 17, 2015.

DTaP, IPV, Hib, PCV and rotavirus vaccinations at his four-month well-baby checkup, and his mother noted that he "seemed a bit sleepier than usual, but otherwise [nothing] unusual." Pet. Ex. 10 at ¶ 4.

On May 11, 2011, C.L. was seen for his six-month well-baby checkup and received DTaP, IPV, Hib, PCV, rotavirus, and Hep B vaccines.[5] Pet. Ex. 4 at 17. At this visit, the pediatrician described C.L. as "[a]lert, interactive, [and] [s]miling." Id. at 16. The pediatrician also noted that C.L. had macrocephaly, which she thought was "likely benign and genetic," but she nonetheless wanted to rule out underlying conditions of the brain. Id. at 17.

C.L.'s mother, father, grandmother, and baby-sitter submitted affidavits in support of the petition. C.L.'s mother stated that receiving his vaccinations on May 11, 2011, C.L. "became very sleepy and fell asleep" in the car. Pet. Ex. 10 at ¶ 9. That afternoon and evening, C.L. was cranky, refused to eat dinner, and went to bed much earlier than usual. Id. at ¶¶ 11-13. C.L. spent the next day with his babysitter, "remained out of sorts," and went to bed a little earlier than usual again. Id. at ¶¶ 14-15.

His parents attested that the following day, May 13, 2011, C.L. did not wake up on his own, which was unusual. Pet. Ex. 10 at ¶ 16; Pet. Ex. 11 at ¶ 9. That morning, C.L.'s father drove him to his grandmother, Suzanne Lord, who had agreed to watch him for the day. Pet. Ex. 11 at ¶ 10. C.L.'s grandmother attested that C.L. took a nap around 10:30 in the morning for about an hour, fell asleep again during a walk outside in a stroller, and remained asleep until about 1:45 pm. Pet. Ex. 12 at ¶¶ 8-10. He was "extremely fussy and crying" when he awoke, and it was unusual for him to "sleep like this up to this point in the day." Id. at ¶¶ 9, 10. Around 3:00 o'clock in the afternoon, C.L. became sleepy again, so she placed him face up in the crib for a nap. Id. at ¶ 12. When she returned to his room around 4:15 pm, she saw him lying in the crib face down. Id. at ¶ 13. Nothing was coming out of his mouth at that time. Id. C.L. was unresponsive when nudged, and when she turned him over on his back, she saw a bluish hue around his eyes and face. Id. at ¶ 14. She tried to perform chest compressions and blow into his mouth, whereupon a "white fluid that seemed like baby formula" came out of his mouth. Id. at ¶ 15.

The police incident report states that Suzanne Lord had been babysitting C.L. and laid him on his back for a nap around 3:00 o'clock in the afternoon. Pet. Ex. 8 at 5. "There was no blanket covering him and there was a small stuffed animal in the corner." Id. at 5, 21. Upon returning to the room at around 3:55PM, she saw that he had "turned onto his stomach and had his arms out to the sides." Id. Ms. Lord told the police that she had never seen C.L. sleep on his stomach. Id. When re-interviewed on May 14, 2014, Ms. Lord was again "adamant" about having placed C.L. in the crib on his back, and reiterated that she found him on his stomach. Id. at 6. He did not respond when nudged, and when she picked him up his face was blue. Id. She said she immediately began doing chest compressions, placed him on the changing table, and dialed 911. Id. When the police arrived, C.L.'s grandmother "pointed out a wet spot where his face had been on the mattress" and said that "when she was blowing into his mouth he spit up some white liquid which she thought was formula." Id. at 5. C.L.'s father stated that there had been several occasions where C.L. would spit up when placed on his stomach on the floor for play time. Id. at 6.

[5] He received the rotavirus vaccine orally, and the other vaccines in his thighs. See Pet. Ex. 4 at 17.

C. L. was transported to Saint Anne's Hospital by the Little Compton and Tiverton Fire/Rescue, and was admitted to the emergency department at 5:22PM on May 13, 2011. Pet. Ex. 6; Pet. Ex. 7 at 1. Efforts to resuscitate him were unsuccessful, and C.L. was pronounced dead on May 13, 2011. Id. at 5; Pet. Ex. 14. The attending physician at Saint Anne's reported finding lividity on C.L.'s back. See Pet. Ex. 7 at 4-5; Pet. Ex. 8 at 5. Dr. Zane, the medical examiner who performed the autopsy on May 15, 2011, also noted posterior lividity.[6] Pet. Ex. 9 at 10.

On autopsy, Dr. Zane ruled the cause of death "[s]udden unexpected infant death of uncertain etiology" and the manner "natural." Pet. Ex. 9 at 9. The parties agree that the characterization of C.L.'s cause of death as sudden infant death syndrome ("SIDS"), is appropriate. Joint Prehearing Submission, filed June 16, 2015, at 1.

The parties' experts in neuropathology, Dr. Miller and Dr. Lidov, reviewed slides of C.L.'s brain. Both experts agreed that the slides showed some nonspecific abnormalities in the frontal white matter, as well as a group of cells that appeared to belong to the inferior olivary nucleus (part of the medulla) located out of place, more dorsally in the brainstem. See Tr. at 11-12, 344-46.

II. SUDDEN INFANT DEATH SYNDROME

Sudden infant death syndrome is defined as "the sudden death of an infant less than [one] year of age that remains unexplained after a complete autopsy, death scene investigation, and review of the clinical history." Pet. Ex. 27 at 2.[7] The majority of deaths occur during "a sleep period." Resp. Ex. A-10 at 1.[8] It is not clear "whether SIDS occurs during sleep itself or during the many transitions between sleep and arousal that occur . . . since [] deaths are typically not witnessed." Id.

SIDS is the leading cause of infant mortality in the United States, with an incidence of about .53 per 1,000 infants. Resp. Ex. C-11 at 3.[9] Research into the causes of SIDS has revealed that the risk of death is twofold in infants who are put to sleep in the prone, i.e. face down, position. Id. Sleeping in the prone position is thought to trigger infant death through "asphyxia due to airway compression or rebreathing of exhaled gases in the face-down position . . . . and compromised arousal in response to asphyxia generated in the prone position." Resp. Ex. A-10 at 2. Other risk factors for SIDS related to the "sleeping environment" have been recognized, including "over-bundling, bed sharing, face down position and soft bedding." Pet. Ex. 27 at 3.

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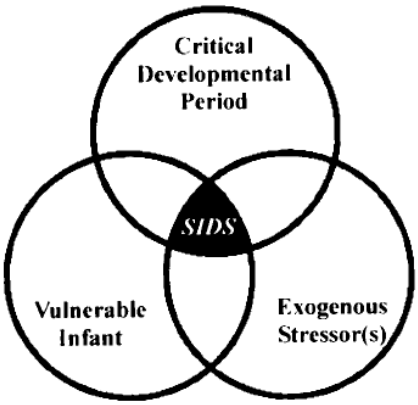
[6] According to the police report, when informed that C.L.'s grandmother reported finding C.L. lying on his stomach, Dr. Zane opined that her account was not inconsistent with the facts of the case. Pet. Ex. 8 at 9. Dr. Zane said that due to the time C.L. was placed in the crib and the time of the call to 911, lividity would have set in after C.L. was moved. Id. at 9.

[7] Pet. Ex. 27, Hannah C. Kinney, *Brainstem Mechanisms Underlying the Sudden Infant Death Syndrome: Evidence from Human Pathologic Studies*, 51 DEV. PSYCHOBIOL. 223 (2009).

[8] Resp. Ex. A-10, Hannah C. Kinney & Bradley T. Thach, *The Sudden Infant Death Syndrome*, 361(8) NEW ENG. J. MED. 795, 798 (2009) (quoting Daniel C. Shannon & Dorothy H. Kelly, *SIDS and Near-SIDS*, 306 NEW ENG. J. MED. 959 (1982)).

[9] Resp. Ex. C-11, Felicia L. Trachtenberg et al., *Risk Factor Changes for Sudden Infant Death Syndrome After Initiation of Back-to-Sleep Campaign*, 129 PEDIATRICS 630 (2012).

In 1994, Dr. Hannah C. Kinney and her colleagues proposed the Triple Risk Model as a way to conceptualize the "emerging multidisciplinary data." Resp. Ex. A-10 at 2. According to this model, SIDS occurs when three factors are simultaneously present: an underlying vulnerability in the infant; a critical developmental period; and an exogenous stressor. Pet. Ex. 25/Resp. Ex. A-7 at 3.[10] The Venn diagram below illustrates the Triple Risk Model:



Id. at 2, Figure 1.

The underlying vulnerability of an infant is affected by intrinsic risk factors, which may be either genetic or environmental. Resp. Ex. A-10 at 4; Resp. Ex. C-11 at 3-4. Intrinsic risk factors include "developmental factors, such as prematurity . . . genetic factors, such as familial SIDS (i.e., a recurrence of SIDS in subsequent siblings), male sex (by a 2:1 ratio), and race or ethnic group." Resp. Ex. A-10 at 4. In addition, "environmental conditions extrinsic to the infant, such as poverty, adverse prenatal exposures to certain substances (e.g. cigarette smoke and alcohol or illicit drugs), and postnatal exposure to cigarette smoke." Id. at 4-5.

Exogenous, or "extrinsic" risk factors, on the other hand, are "physical stressors that [] place a vulnerable infant at risk for asphyxia or other homeostatic derangement." Resp. Ex. A-10 at 4. These factors include "prone and side-sleeping positions, bedclothes that cover the head, sleeping on sofas or other soft furniture in which the infant could become wedged, a high ambient temperature in the sleeping environment, soft bedding, and bed sharing." Id. The prone sleeping position is still associated with 30% to 50% of SIDS cases and another 50% occur where infants are "sharing a bed, sofa, or sofa chair with another person." Id. Another extrinsic risk factor is mild infection, including colds or upper respiratory tract infections. Id.; Resp. Ex. C-11 at 4.

"The occurrence of extrinsic risks in virtually all SIDS deaths implies that SIDS is precipitated by a 'trigger' at the time of death. These extrinsic risk factors are consistent with asphyxia-generating conditions, e[.]g[.], face-down position, prone position, and adult mattress." Resp. Ex. C-11 at 5. Studies have shown that having multiple risk factors significantly increases the risk of SIDS. In a 2012 article by Trachtenberg, et al.,[11] the authors studied 568 SIDS deaths from

[10] Pet. Ex. 25/Resp. Ex. A-7, Hannah C. Kinney et al., *Medullary Serotonergic Network Deficiency in the Sudden Infant Death Syndrome: Review of a 15-Year Study of a Single Dataset*, 60 J. NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY 228 (2001).

[11] Resp. Ex. C-11, Trachtenberg, *supra* note 8 at 635.

the San Diego Medical Examiner's Office from 1991 to 2008 and found that the "majority of SIDS infants were subject to at least 2 extrinsic risk factors." Resp. Ex. C-11 at 7.

The mechanism of death of SIDS has been thought to be related to a failure of the "autonomic regulation of cardiovascular or respiratory activity or both." Resp. Ex. A-10 at 5. There is "compelling evidence for a respiratory pathway in the majority of SIDS deaths." Id. The "respiratory pathway to SIDS" can be described in five steps. Id. The infant first has a "life-threatening event," which may occur in any infant during sleep, which causes "severe asphyxia, brain hypoperfusion, or both." Id. Examples of life-threatening events include "rebreathing of exhaled gases in the face-down position . . . reflex apnea originating from the laryngeal chemoreflex, and obstructive apnea due to gastric regurgitation." Id. Second, the "vulnerable infant does not wake up and turn his or her head in response to asphyxia . . . resulting in rebreathing or an inability to recover from apnea." Id. "Third, progressive asphyxia leads to a loss of consciousness and areflexia, a so-called hypoxic coma." Id. Fourth, the infant develops "extreme bradycardia and hypoxic gasping." Id. Fifth and finally, there is a failure of autoresuscitation due to ineffective gasping that leads to "uninterrupted apnea and death." Id. The increased risk of SIDS in infants younger than six months is probably due to "immature homeostatic systems" and "developmental motor mechanisms," such as the inability of an infant to lift and turn his or her head in the prone position. Id. at 7-8.

Research on the "underlying vulnerability" present in infants who die of SIDS has focused on the area of the brainstem responsible for autonomic function and respiration. Resp. Ex. A-10 at 7. This research suggested that 50% to 75% of infants who die of SIDS may have a neurochemical abnormality in the "medullary 5-hydroxytryptamine system," ("5-HT system"), which modulates and integrates many different homeostatic functions, including "ventilation and gasping . . . responses to carbon dioxide and oxygen, [and] arousal from sleep." Id. This vulnerability has also been described as a "deficiency in the neurotransmitter serotonin [5-HT] in [the] brainstem regions that help mediate protective responses to homeostatic stressors such as asphyxia…" Resp. Ex. C-11 at 5. The area of defect is referred to as the "medullary 5-HT system," which is comprised of "5-HT neuronal cell bodies" located in the medulla. Pet. Ex. 27 at 4. Animal research indicated that 5-HT "influences multiple homeostatic functions mediated by the medulla," including "central chemoreception to carbon dioxide and/or oxygen . . . cardiovascular function . . . upper airway control . . . [and] respiratory rhythm generation." Id. at 4-5. Kinney and her colleagues believed that there is a "subclinical autonomic dysfunction associated with SIDS" related to abnormalities of the "medullary 5-HT system," which is seen on autopsy. Id. at 5. They hypothesized that the medullary 5-HT defect originates in utero during the period of development and differentiation of the brainstem. Id. at 7. They also believed that "sudden death in SIDS likely results from a complex interaction of several/multiple dysfunctional neurotransmitter systems in the brainstem, and that death is triggered by homeostatic stressors during sleep in a vulnerable developmental period." Id. at 8.

III. STANDARDS FOR ADJUDICATION

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and

generosity.'" Rooks v. Sec'y of Health & Human Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioners' burden of proof is by a preponderance of the evidence. § 300aa-13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, petitioners must prove that that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner who satisfies this burden is entitled to compensation unless respondent can prove, by a preponderance of the evidence, that the vaccine's injury is "due to factors unrelated to the administration of the vaccine." § 300aa-13(a)(1)(B).

IV. EXPERT OPINIONS AND CAUSATION ANALYSIS

A. Issue

The parties agree that the sole issue to be resolved is "[w]hether the vaccines that C.L. received on May 11, 2011, caused or substantially contributed to his death." (citations omitted). See Joint Prehearing Submission, filed June 16, 2015, at 2.

B. Legal Framework

To receive compensation under the Program, petitioners must prove either: (1) that C.L. suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table— corresponding to a vaccine that he received, or (2) that C.L. suffered an injury that was actually caused by a vaccination. See §§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Petitioners must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because petitioners do not allege that C.L. suffered a Table injury, they must prove that the vaccines C.L. received caused his death. To do so, they must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and his injury ("Althen Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for his injury ("Althen Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and his injury ("Althen Prong Three"). § 300aa–13(a)(1); Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

The causation theory must relate to the injury alleged. Thus, petitioners must provide a reputable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioners cannot establish entitlement to compensation based solely on their assertions. Rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 300aa-13(a)(1). In determining whether petitioners are entitled to compensation, the special master shall consider all

material contained in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 300aa-13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' offered experts and rule in petitioners' favor when the evidence weighs in their favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence"); Althen, 418 F.3d at 1280 ("close calls" are resolved in petitioner's favor).

Another important aspect of the causation-in-fact case law under the Vaccine Act concerns the factors that a special master should consider in evaluating the reliability of expert testimony and other scientific evidence relating to causation issues. In Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579 (1993), the United States Supreme Court listed certain factors that federal trial courts should utilize in evaluating proposed expert testimony concerning scientific issues. In Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999), the Federal Circuit ruled that it is appropriate for special masters to utilize Daubert's factors as a framework for evaluating the reliability of causation-in-fact theories actually presented in Program cases.

The Daubert factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." Terran, 195 F.3d at 1316 n.2 (citing Daubert, 509 U.S. at 592-95). In addition, where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357, 1362 (Fed.Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 743 (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 146 (1997)).

C. Althen Analysis

(1) Althen Prong One: Petitioners' Medical Theory

Under Althen Prong One, petitioners must set forth a medical theory explaining how the vaccines could have caused C.L.'s death. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009); Pafford, 451 F.3d at 1355-56.

Petitioners' theory of causation must be informed by a "sound and reliable medical or scientific explanation." Knudsen, 35 F.3d at 548; see also Veryzer v. Sec'y of Health & Human Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 300aa- 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If petitioners rely upon a medical opinion to support their theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen, 618 F.3d at 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed.

Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it.") (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980)).

a. Petitioners' Expert Dr. Douglas Miller

Dr. Douglas Miller earned his medical degree from the University of Miami School of Medicine in 1978. Curriculum Vitae of Dr. Douglas C. Miller, Pet. Ex. 46 at 1. He received a Ph.D. in physiology and biophysics from the University of Miami in 1980. Id. Dr. Miller was a resident at Massachusetts General Hospital from 1980-1984, focusing in the areas of anatomic pathology and neuropathology. Id. Currently, he serves as a clinical professor of pathology and anatomical sciences at the University of Missouri School of Medicine, and is also the program director of pathology residency. Id. at 3. In addition, he is an associate medical examiner for Boone, Callaway, and Greene Counties in Missouri. Id.; Tr. at 6.

Dr. Miller used the Triple Risk Model for SIDS[12] as a framework for his proposed theory of causation. Tr. at 17-21. He explained that in the Triple Risk Model, an infant in a critical stage of development (the first year of life), with an intrinsic vulnerability in the form of a brainstem abnormality affecting the serotonin network, encounters one or more extrinsic stressors, such as prone sleeping position, and an elevated level of carbon dioxide results. Id. at 18-20. An infant with a defective serotonin network then fails to sufficiently arouse themselves and breathe. Id. at 20-21.

Dr. Miller stated that infants may have an intrinsic vulnerability because of "brainstem abnormalities which lead to deficiencies in serotonin-mediated synaptic activity, from the arcuate nuclei or other brainstem serotoninergic nuclei." Expert Peport of Dr. Douglas C. Miller, Pet. Ex. 22 at 7. "A significant proportion of SIDS cases have histopathological or biochemical abnormalities in the medulla, the lowest part of the brainstem." Id. at 6; Tr. at 16-17. The medulla is "responsible for the initiation and regulation of muscle efforts underlying breathing," and regulation of heart rate. Pet. Ex. 22 at 6. The 5-HT system in the medulla is a network that uses serotonin as an excitatory neurotransmitter, and is linked to respiration, particularly arousal from sleep and sleep apnea through increased respiration. Tr. at 25. In tandem with the inhibitory network of GABAergic neurons, the medullary 5-HT serotonergic system works to keep homeostasis. Id. at 24-25. Dr. Miller opined that a deficiency in the medullary 5-HT system would affect an infant's ability to arouse and breathe in response to elevated levels of carbon dioxide encountered due to an external stressor. Id. at 25-26.

In addition, Dr. Miller opined that prematurity would be an intrinsic risk factor, because "the presumption would be that the nervous system's development in the medulla is even more immature because of prematurity than in an equivalent aged full-term baby. . . . So that there's even less ability to respond." Tr. at 27-28 (stating that the articles filed as Pet. Exs. 55 and 56[13] show that

[12] See Pet. Ex. 25/Resp. Ex. A-7, Kinney, *supra* note 9 at 228-247.

[13] Pet. Ex. 55, Jackie Lee et al., *Frequency of Apnea, Bradycardia, and Desaturations Following First Diphtheria-Tetanus-Pertussis-Inactivated Polio-Haemophilus Influenzae Type B Immunization in Hospitalized Preterm Infants*, BMC PEDIATRICS (2006), *available at* http://www.biomedcentral.com/1471-2431/6/20; Pet. Ex. 56, Sven Schulzke et al., *Apnoea [sic] and Bradycardia in Preterm Infants Following Immunisation with Pentavalent or Hexavalent Vaccines*, 164 EUR. J. PEDIATR. AT 432 (2005).

following vaccination, there was an increased incidence of nonfatal apnea and bradycardia in premature infants).

One recognized extrinsic risk factor for SIDS is mild infection, such as an upper respiratory infection ("URI") or gastrointestinal infection ("GI infection"). Tr. at 31. Dr. Miller opined that infection does not operate as a mechanical risk factor, but rather that the peripheral cytokines produced by the innate immune response to infection communicate with the nervous system to produce the risk for SIDS. Id. at 31, 240. In other words, infection operates as a "neurochemical" risk factor. He explained that infection stimulates the production of peripheral cytokines, which can have central nervous system effects, such as fever. Id. at 33. He stated that some of these cytokines—the predominant ones produced in response to an infection, such as IL1β, TNF-α, and IL-6—are active in the medulla in modulating synaptic activity of the serotonin and GABAergic networks, and can interact to suppress or reduce the firing of serotonin neurons and increase the firing of inhibitory GABA neurons, thereby reducing the medulla's response to apnea or rising carbon dioxide levels or hypoxia (low levels of oxygen) in the short term.[14] Id. at 33-34, 37-39. In an infant with a defective brainstem, who has reduced levels of 5-HT activity to begin with, the cytokine-caused inhibition can reduce response to the point that the infant does not recover from apnea, hypoxia, or excessive carbon dioxide levels. Id. at 39. In support of the proposition that mild infections can act as an external stressor via cytokine interaction with the CNS, Dr. Miller cited articles by Rognum, Kadhim, and Vege.[15]

Other than upper respiratory and gastrointestinal infections, Dr. Miller could not identify any other infections that have been identified as a risk factor for SIDS. Tr. at 89. Fever, he noted, can be caused by other types of infection, and he believed fever was in and of itself an independent risk factor for SIDS.[16] Id. at 87-89.

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[14] Dr. Miller acknowledged that the Chen and Miller article, submitted by Dr. McCusker, indicates that immune stimulation can result in increases in 5-HT, and therefore augmentation of the arousal mechanism. Tr. at 40 (referencing Resp. Ex. C-15, Guo-Lin Chen & Gregory M. Miller, *Advances in Tryptophan Hydroxylase-2 Gene Expression Regulation: New Insights into Serotonin—Stress Interaction and Clinical Implications*, 159B AM. J. OF MEDICAL GENETICS 152 (2012)). However, he stated that this increase takes time to occur, and would occur hours after a stimulus, whereas in the context of an immediate hypoxic event resulting in death within minutes to an hour, there would not be enough time for the feedback loop to effect this result. Tr. at 41, 135 (citing Pet. Ex. 61, Jianping Wang & Adrian J. Dunn, *Mouse Interleukin-6 Stimulates the HPA Axis and Increases Brain Trytophan and Serotonin Metabolism*, 33 NEUROCHEM. INT. 143 (1998)).

[15] Pet. Ex. 36, Ingvar Rognum et al., *Interleukin-6 and the Serotonergic System of the Medulla Oblongata in the Sudden Infant Death Syndrome*, 118 ACTA. NEUROPATHOL. 519 (2009); Pet. Ex. 34, Hazim Kadhim et al., *Distinct Cytokine Profile in SIDS Brain: A Common Denominator in a Multifactorial Syndrome?*, 61 NEUROLOGY 1256 (2003); Pet. Ex. 39, Ashild Vege & Torleiv Ole Rognum, *Sudden Infant Death Syndrome, Infection and Inflammatory Responses*, 42 FEMS IMMUN. & MED. MICROBIOL. 3 (2004).

[16] In support of this, Dr. Miller cited the following: Pet. Ex. 27, Hannah C. Kinney, *Brainstem Mechanisms Underlying the Sudden Infant Death Syndrome: Evidence from Human Pathologic Studies*, 51 DEV. PSYCHOBIOL. 223, 223 (2009) (In this article, hyperthermia is listed as an extrinsic stressor, which Dr. Miller said is the same thing as fever. Tr. at 139. Dr. McCusker testified that hyperthermia could be caused by factors such as overbundling. Id. at 193); Pet. Ex. 39, Ashild Vege & Torliev Ole Rognum, *Sudden Infant Death Syndrome, Infection and Inflammatory Responses*, 42 FEMS IMMUN. & MED. MICROBIOL. 3, 4 (2004) (Discusses the Triple Risk Model and hyperthermia as a component of the vicious cycle of SIDS); Pet. Ex.

In support of his position that the 5-HT system is critical for recovery from apnea and that certain cytokines play a role in reducing recovery from apnea, Dr. Miller cited studies by Stoltenberg, Froen, and Brambilla.[17] Tr. at 70. As for the mechanism of interaction between the peripheral cytokines and the central nervous system, he stated that the peripheral cytokines "probably cross the blood-brain barrier, although there are proposals whereby [they] might signal across it without actually getting to it, but have an interaction with the central nervous system that is a physiological synaptic interaction rather than an inflammatory interaction." Id. at 35. Dr. Miller stated that this process would not produce inflammation in the brain, as the cytokine action is one of physiological neurotransmitter modulation, not inflammatory activity. Id. at 35, 81.

Reaching outside of the traditional extrinsic risk factors listed in the Triple Risk Model of SIDS, Dr. Miller testified that vaccines could be an extrinsic risk factor contributing to SIDS. Tr. at 41. He acknowledged, however, that Dr. Kinney has not studied vaccinations in relation to SIDS. Id. When asked whether he was the first medical professional, outside of the Vaccine Program, to assert that vaccination is an external risk factor in Dr. Kinney's triple risk model, Dr. Miller said that it had not been done "in the specific terms of Dr. Kinney's research," but that there is "abundant literature associating vaccinations with SIDS." Id. at 92. He asserted that he had cited literature from multiple people that associated vaccines as a possible mechanism leading to SIDS. Id. at 92-93. When asked to cite a particular paper where someone has postulated that an external risk factor for SIDS is vaccination, he cited a case report by Balci,[18] in which he thought the authors suggested vaccines were an external risk factor under the Triple Risk Model in the sudden unexpected death of twin infants shortly post-vaccination, based on the proximity in time of death to vaccination. Id. at 91-95. Dr. Miller also noted that a case report by Ottaviani[19] mentions that one of the triggers of SIDS in that case could have been vaccination. Id. at 141-42. In his written report, he cited several additional papers reporting cases of SIDS following infant vaccinations. See Pet. Ex. 22 at 7. When pressed, however, Dr. Miller admitted that he was not sure anyone has "connected all those dots" between cytokines, cytokine production by vaccines, and vaccines specifically being a risk factor for SIDS in vulnerable infants. Tr. at 96. And, in fact, the Balci authors themselves specifically note that "studies have shown that vaccinations are not associated with an increased risk of SIDS." Pet. Ex. 58 at 5.

37, Kadhim et al. *Interleukin-2 as a Neuromodulator Possibly Implicated in the Physiopathoogy of Sudden Infant Death Syndrome*, 480 NEUROSCIENCE LETTERS 122, 122 (2010) (Says SIDS victims often have preceding mild infections inflammatory conditions, like post-vaccinal fever).

[17] Pet. Ex. 32, Lauritz Stoltenberg et al., *Changes in Apnea and Autoresuscitation in Piglets After Intravenous and Intrathecal Interleukin-1β Injection*, 22 J. PERINAT. MED. 421 (1994); Pet. Ex. 33, J. Frederik Froen et al., *Adverse Effects of Nicotine and Interleukin-1β on Autoresuscitation After Apnea in Piglets: Implications for Sudden Infant Death Syndrome*, 105 PEDIATRICS (2000); Pet. Ex. 35, D. Brambilla et al., *Interleukin-1 Inhibits Firing of Serotonergic Neurons in the Dorsal Raphe Nucleus and Enhances GABAergic Inhibitory Post-Synaptic Potentials*, 26 EUR. J. NEUROSCIENCE 1862 (2007).

[18] Pet. Ex. 58, Yasemin Balci et al., *Simultaneous Sudden Infant Death Syndrome*, 14 J. OF FORENSIC AND LEGAL MED. 87 (2007).

[19] Pet. Ex. 42, Giulia Ottaviani et al., *Sudden Infant Death Syndrome (SIDS) Shortly After Hexavalent Vaccination: Another Pathology in Suspected SIDS?*, 448 VIRCHOWS ARCH 100 (2006).

Dr. Miller opined that vaccinations are analogous to mild infection as an extrinsic risk factor. Tr. at 42-43. A vaccination, he said, activates the immune system to produce peripheral cytokines in the same way as a mild infection—the same cytokines reach the same peaks in the same time interval in children who have been vaccinated as in children who have influenza infections—and these cytokines have the same effect on the nervous system as those produced by infection. Id. at 42-43, 80. In support of the contention that the cytokine levels and effects provoked by vaccination are not significantly different than those provoked by infection, Dr. Miller cited an article by Kashiwagi et al.[20] The Kashiwagi article discusses an association between the DTaP and Hib vaccinations, which C.L. received, to the production of cytokines IL-1β, IL-6 and TNF-α—the same cytokines that are produced by infection and those that petitioners theorize are implicated in their interpretation of the Triple Risk Model. The study compared levels of cytokines[21] in the blood serum of vaccine recipients with and without febrile reactions within 24 hours of vaccination. There was no significant difference between the two groups except that the cytokine G-CSF was elevated in individuals with a febrile illness. The significance of this finding was not determined. In fact, the authors stated that cytokine production due to vaccines has "not been sufficiently investigated." Pet. Ex. 52 at 3.

During the hearing, Dr. Miller discussed and criticized a number of the epidemiological studies cited by respondent's experts.[22] Dr. Miller stated that in principle, it ought to be possible for epidemiological studies to detect vaccination as a risk factor for SIDS, but that with the notable exception of the Traversa[23] study, "the [epidemiological] studies done to date have not had the sort of rigorous definition of populations that are necessary to draw appropriate conclusions [regarding vaccination as a risk factor for SIDS]." Tr. at 48, 54-55. Dr. Miller said that the Traversa authors emphasized that a complete neuropathological evaluation, including a detailed examination of brainstem structure on autopsy, was necessary in order to identify those infants who were at risk because of a developmental abnormality of the brainstem. Id. at 54-55.

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[20] Pet. Ex. 52, Yasuyo Kashiwagi et al., *Production of Inflammatory Cytokines in Response to Diphtheria-Pertussis-Tetanus (DPT), Haemophilus Influenza Type B (Hib), and 7-Valent Pneumococcal (PCV7) Vaccines*, 10 HUM VACCINE IMMUNOTHER. 677 (2014).

[21] These cytokines include IL-1β, IL-4, IL-6, IL-10, IL-12, IFN-y, MIP-1, TNF-α, PGE2, and G-CSF.

[22] For Dr. Miller's full critique of respondent's literature, see Tr. at 47-69.

[23] Pet. Ex. 43/Resp. Ex. A-13, Giuseppe Traversa et al., *Sudden Unexpected Deaths and Vaccinations During the First Two Years of Life in Italy: A Case Series Study*, PLOS ONE 2011; 6E 16363 (2011). The Traversa study was a response to an anecdotal report from Germany of an association between vaccination with a hexavalent vaccine in the second year of life and sudden unexpected death in the two days following vaccination. Traversa, Pet. Ex. 43 at 1 (referencing Pet. Ex. 40/Resp. Ex. A-14, Rudiger von Kries et al., *Sudden and Unexpected Deaths After the Administration of Hexavalent Vaccines (Diphtheria, Tetanus, Pertussis, Poliomyelitis, Hepatitis B, Haemophilius Influenzae Type B): Is There a Signal?*). In the Traversa study, the statistically significant increased relative risk was one tenth the size of the effect observed in Germany, was confined to the first dose, and "may be partly explained by a residual uncontrolled confounding effect of age." Id.

b. Petitioners' Expert Dr. James Oleske

Dr. James Oleske received his medical degree from the College of Medicine and Dentistry of New Jersey in 1971. Curriculum Vitae of Dr. James Oleske, Pet. Ex. 51 at 1. From 1971 to 1974, he served as a pediatric resident and then a pediatric ambulatory care fellow with the College of Medicine and Dentistry of New Jersey. Id. He then completed a pediatric infectious disease and immunology fellowship at Emory University Medical School. Id. at 2. Dr. Oleske received a master's degree in Public Health from Columbia University in 1974. Id. at 1. He is licensed to practice medicine in New Jersey, with specialties in pediatrics and diagnostic laboratory immunology. Id. at 2. Dr. Oleske is certified by the American Board of Pediatrics and the American Board of Allergy and Immunology. Id. at 2. He worked with the Brighton Group, which is a group led by the centers for Disease Control and Prevention ("CDC") that focuses on issues of vaccine safety. Id. at 9. Currently, Dr. Oleske serves as the director of the division of allergy, immunology, and infectious diseases at Rutgers University - New Jersey Medical School. Expert Report of Dr. James Oleske, Pet. Ex. 50 at 7.

Dr. Oleske was not called as a witness at the hearing but submitted an expert report in this case. See Pet. Ex. 50. Like Dr. Miller, his proposed medical theory to explain how the vaccines at issue can cause death was premised on the Triple Risk Model. Id. at 3-4. In this model, "extrinsic and intrinsic risk factors converge in a young infant during a vulnerable window of time" when "the still immature, developing brain lacks the adaptive responses to adequately control postnatal homeostasis." Id. at 3. Dr. Oleske stated that studies by the Kinney group have demonstrated that infants with SIDS have a latent defect(s) in the medullary serotonergic system, the part of the brain that controls autonomic functions, including respiration. Id. at 4. "The normal developmental immaturity in homeostasis prevents the 'at risk' infant from successfully responding to a number of exogenous and endogenous stressors, which ultimately affects critical respiratory and arousal functions." Id. at 4. The infant then stops breathing, and "a disturbance in the usual balance of cytokine activity in the arcuate nucleus blocks rather than stimulates a normal arousal signal," so that the infant suffocates. Id.

Dr. Oleske opined that in the Triple Risk Model, "there is support for the role of cytokines as mediators for such failures of respiratory/arousal functions in a susceptible infant during this window of vulnerability after immunization." Pet. Ex. 50 at 4. He stated that "[i]t is now accepted that pathological conditions, such as cancers, viral infections, and autoimmune diseases, are associated with abnormal cytokine production." Id. at 5. He said that even if "brain cytokines are neuroprotective when they are functioning under normal circumstances . . . . in the vulnerable infant, experiencing one or more extrinsic factors, the antigen load of vaccines and adjuvants, can become neurodamaging and provide the 'perfect storm' for SIDS." Id. He said that because of the absence of negative feedback control occurring in the developing brain of a vulnerable infant at risk for SIDS, a given cytokine "may flood and accumulate in the extracellular compartment of tissues thereby impairing the cytokine network homeostasis and contributing to local pathogenesis." Id. at 5-6.

In support of his position that cytokines play a causative role in SIDS, Dr. Oleske cited two studies which were also cited by Dr. Miller. First, he cited a study by Kadhim,[24] which showed an increased level of the cytokine IL-1β in brains of children who died of SIDS. Pet. Ex. 50 at 5. Dr. Oleske said that in that 2003 study, the authors postulated that brain injury, such as occurs with infection and inflammation,[25] could lead to alterations in the cytokine-neurotransmitter interactions, leading to changes in the center controlling oxygen/carbon dioxide balance, in turn leading to SIDS. Id. Dr. Oleske also cited a 2004 study by Vege,[26] in which the authors suggested that a slight infection could increase the risk of SIDS by inducing cytokine IL-6, which in turn increases temperature, which then affects respiration. Id.

Like Dr. Miller, Dr. Oleske expanded on the Triple Risk Model in a novel way, arguing that vaccinations act as extrinsic risk factors analogous to the way the infections act as extrinsic risk factors—by interfering with the complex cytokine signaling in the brain. Pet. Ex. 50 at 5.

c. Respondent's Expert Dr. Christine McCusker

Dr. Christine McCusker earned a Master of Science in 1988, followed by an M.D in 1993, at McMaster University, in Hamilton, Ontario. Curriculum Vitae of Dr. Christine McCusker, Resp. Ex. D at 2. Her residency training was in pediatrics, at Montreal Children's Hospital, McGill University, from 1993-1996. Id. at 3. She was then a clinical fellow in allergy and immunology at McGill University from 1996-1999. Id. Dr. McCusker is board certified in pediatrics. Id. She is now a pediatric allergist/immunologist, and sees patients at an allergy and immunology clinic. Tr. at 152. She also does clinical and fundamental research in immunology, runs the clinical immunology laboratory at McGill, and is division head of the Pediatric Department of Allergy, Immunology, and Dermatology. Id. at 151-52. In addition, she teaches medical students in the areas of immunology, dermatology, and malignant hematology. Id. at 153.

Dr. McCusker did not agree with petitioners' experts that vaccines act as an extrinsic risk factor under the Triple Risk Model of SIDS. She noted that vaccines have not been identified by Kinney as an external stressor. Tr. at 200. Dr. McCusker stated that recognized extrinsic factors—"prone and side-sleeping, bed sharing, over-bundling, soft bedding, face covered and recent history of upper respiratory tract infection" contribute to the risk for SIDS by effecting a mechanical change in an infant's ability to respire, as opposed to a neurochemical change. Expert Report of Christine McCusker, Resp. Ex. C at 5. These are factors that have "the potential to shift the oxygen

[24] Dr. Oleske did not include a citation to this source, but it appears to be Pet. Ex. 34, Hazim Kadhim et al., *Distinct Cytokine Profile in SIDS Brain: A Common Denominator in a Multifactorial Syndrome?*, 61 NEUROLOGY 1256 (2003).

[25] Dr. Olekse thus seems to suggest that inflammation may play a causal role, whereas Dr. Miller disagrees. Dr. Miller testified that the cytokine action at issue is not inflammatory. See Tr. at 35, 81.

[26] Again, Dr. Oleske did not include a citation to this source, but it appears to be Pet. Ex. 39, Ashild Vege & Torleiv Ole Rognum, *Sudden Infant Death Syndrome, Infection and Inflammatory Responses*, 42 FEMS IMMUN. & MED. MICROBIOL. 3, 4 (2004).

and carbon dioxide balance." Id. at 4 (citing Kinney[27]). She testified that URIs in infants mechanically impede an infant's ability to breathe. Tr. at 185. Infants breathe through their noses, and congestion caused by a URI obstructs their nose and—because the reflex to breathe through their mouth instead does not happen easily for them—nasal congestion contributes to a mechanical impediment to breathing. Id. at 184-85. Dr. McCusker stated that there is no literature to support the position that URIs are known to affect SIDS through the mediation of cytokines. Id. at 202. Dr. McCusker testified that there is literature that addresses the issue of whether infection could be a neurochemical risk factor—in particular, she noted a study by Ferrante,[28] which researched whether there are variations in cytokine or immune-related genes in SIDS that would explain the vulnerability of SIDS infants to infection. Tr. at 273. However, the Ferrante study concluded that more studies were needed to understand the interplay between different genetic variations and how they may contribute to an unfavorable immunologic response. Pet. Ex. 53 at 7. Thus, Dr. McCusker disagreed with petitioners' experts' comparison of vaccination to a URI.

Dr. McCusker agreed that the Kashiwagi[29] study, cited by petitioners for the contention that cytokine levels and effects provoked by vaccination are not significantly different than those provoked by infection, demonstrates that cytokines are released in response to vaccination. See Tr. at 231. However, because the study showed that in general, cytokine levels were the same in children with and without fever, Dr. McCusker opined that the interaction of those cytokines in both the periphery and the CNS must somehow qualitatively differ, leading to differing responses. Tr. at 326. In other words, the study demonstrates that it is not just the presence of a certain level of cytokines alone that determines how the CNS responds. Rather, other regulatory factors must come into play, and the interaction (of cytokines on the CNS) could be very much dependent on the event leading to the cyoktine production (i.e. vaccination versus infection). Id. Moreover, the study was not designed to examine the effects of cytokines in the brain following vaccination.

Dr. McCusker agreed with petitioners' experts that the literature suggests that the 5-HT system is implicated in SIDS. Tr. at 190. In infants not intrinsically at risk for SIDS (infants with normal homeostatic networks), the mechanical extrinsic stressors would activate the protective mechanisms in the brain through the 5-HT system, and correct the respiratory problem. Resp. Ex. C at 6. Dr. McCusker explained that Kinney has set forth the hypothesis that in an infant with a defective 5-HT system, however, the neurons may require excessive cytokine stimulation to respond to hypercapnia. Tr. at 201; Resp. Ex. C at 4, 5 (discussing Kinney[30]). The increased levels of cytokines in the SIDS brain are a response to having too much carbon dioxide in the body. Tr. at 201. Dr. McCusker noted, however, that vaccination does not affect carbon dioxide levels. Id. at 202.

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[27] Pet. Ex. 28, Hannah C. Kinney et al., *The Serotonergic Anatomy of the Developing Human Medulla Oblongata: Implications for Pediatric Disorders of Homeostasis,* 41 J. OF CHEMICAL NEUROANATOMY 182 (2011).

[28] Pet. Ex. 53, Linda Ferrante & Siri Hauge Opdal, *Sudden Infant Death Syndrome and the Genetics of Inflammation*, 6 FRONTIERS IN IMMUNOLOGY 1 (2015).

[29] Pet. Ex. 52, Kashiwagi, *supra* note 19.

[30] Pet. Ex. 28, Kinney, *supra* note 26.

However, Dr. McCusker did not agree with petitioners' experts' theory that the expression of cytokines in the brain contributes to a failure to arouse, thus causing SIDS. Tr. at 179. First, there is no evidence that the levels of cytokines detected in the brains of SIDS infants are pathologically elevated, as opposed to elevation found in normal brain homeostasis. Id. She explained that the view that cytokines found in the brain are pro-inflammatory has changed, and it is now understood that they operate as signals of stress in normal brain function, rather than cause inflammation. See id. at 172-77. Dr. McCusker discussed an article by Ron-Harel,[31] which sets forth the current thinking. She explained that early research focused on looking at cytokines in pathological states, such as brain infection or autoimmune diseases, and found that they were elevated in such states. Id. at 172. More recently, however, research has focused on the role of cytokines in normal brain function, and it has become clear that the brain uses cytokines as a homeostatic mechanism and normal communication molecules to indicate stress. Id. at 172-73; Resp. Ex. C at 3. In the brain, cytokines such as IL-1β and IL-6, which can have a pro-inflammatory effect in the periphery, are associated with normal brain function. Tr. at 173-75. Exogenous stimuli or stressors result in upregulation of cytokines in the central nervous system. Id. at 172. Thus, Dr. McCusker stated that the literature suggests that the expression of cytokines in the SIDS brain is a response to stress. Id. at 179, 182, 200 (citing Kinney[32]). The presence of an increased level of cytokines in the arcuate nucleus of SIDS infants "occur[s] as a response to the inciting event rather than an element etiologically linked to the respiratory failure in the vulnerable child." Resp. Ex. C at 5 (referencing Pet. Ex. 36[33]).

Second, Dr. McCusker testified that what is known about cytokines does not suggest that they prevent arousal. Tr. at 179-80. Rather, in the context of sleep, IL-1β and TNF-α have been implicated as arousal molecules, with regard to increasing arousal from REM sleep. Id. at 177-78; 204-08 (discussing Resp. Ex. C-7, C-8, C-9, C-15[34]). Evidence suggests that "the central functions of the cytokines IL1β, IL6 and TNFα at times of infection are to promote fever and to affect the sleep architecture by increasing NREM versus REM sleep resulting in more disturbed sleep with more frequent arousal while permitting the maintenance of increased body temperature." Resp. Ex. C at 4. This means that cytokines improve, rather than impair, autoresuscitation. Tr. at 208.

Third, Dr. McCusker testified that cytokine production in response to a vaccination is localized and "does not generate significant systemic signaling." Tr. at 157-70. Dr. McCusker testified that cytokine expression is tightly regulated—cytokine responses occur locally, and

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[31] Resp. Ex. C-3, Noga Ron-Harel et al., *Brain Homeostasis is Maintained by "Danger" Signals Stimulating a Supportive Immune Response Within the Brain's Borders*, 25(5) BRAIN, BEHAV. IMMUN. 1036 (2011).

[32] Pet. Ex. 28, Kinney, *supra* note 26.

[33] Pet. Ex. 36, Ingvar J. Rognum et al., *Interleukin-6 and the Serotonergic System of the Medulla Oblongata in the Sudden Infant Death Syndrome*, 118 ACTA. NEUROPATHOL. 519 (2009).

[34] Resp. Ex. C-7, Luca Imeri & Mark R. Opp, *How (and Why) the Immune System Makes Us Sleep*, 10 REVIEWS NEUROSCIENCE 199 (2009); Resp. Ex. C-8, James M. Clinton et al., *Biochemical Regulation of Sleep and Sleep Biomarkers*, 7 J. OF CLINICAL SLEEP MED. S38 (2005); Resp. Ex. C-9, Charlene E. Gamaldo et al., *The Sleep-Immunity Relationship*, 30 NEUROL. CLIN. 1313 (2012); Guo-Lin Chen & Gregory M. Miller, *Advances in Tryptophan Hydroxylase-2 Gene Expression Regulation: New Insights into Serotonin—Stress Interaction and Clinical Implications*, 159B AM. J. OF MEDICAL GENETICS 152 (2012).

generally do not generate significant systemic signaling. Id. at 157, 179-81. However, they can have systemic effects if the stimulus is sufficient, which can be evidenced by sickness behaviors such as fever, fatigue, and irritability. Id. at 159. Dr. McCusker stated that fever comes up as a co-factor in many studies but has not been individually identified as an extrinsic risk factor itself. Id. at 192. Fever is mediated by IL-1, IL-6, and TNF-α. Id. at 263. In cases where systemic effects do occur, they happen when cytokine signaling reaches the blood brain barrier and signals through it to upregulate cytokines produced in the brain. Id. at 160. She stated that most cytokines probably do not actually cross the blood brain barrier, and therefore the peripheral cytokines do not flood into the brain. Id. at 161. Again, the presence of increased cytokines in the brain signifies the response to stress rather than a cause of respiratory failure. Resp. Ex. C at 5.

With regard to the epidemiology literature assessing a potential causal connection between vaccination and SIDS, Dr. McCusker testified that there have been several studies that have looked at whether or not there is an increased frequency of SIDS associated with vaccination in a way other than temporal, but she does not find any of the large studies (as opposed to case series and case reports) supportive of the hypothesis that vaccines are implicated. Tr. at 212-13. She opined that the epidemiological studies performed to date have been sufficient to pick up risk factors such as position, URI, and reflux. Id. at 213. Given that vaccinations are likely to occur more frequently than URIs in children under the age of six months, she would expect these studies to pick up vaccines as a risk factor. Id. at 213-14. However, the studies have not done so.

d. Respondent's Expert Dr. Hart Lidov

Dr. Hart Lidov received a Ph.D. from Johns Hopkins University in 1980, followed by a medical degree in 1982. Curriculum Vitae of Dr. Hart G.W. Lidov, Resp. Ex. B at 1. From 1983 to 1991, Dr. Lidov was a resident in pediatrics and neurology at Massachusetts General Hospital, and a neuropathology and anatomic pathology resident at Brigham and Women's Hospital. Id. He has a special qualification in child neurology from the American Board of Psychiatry and Neurology. Id. at 2. Dr. Lidov presently serves as a staff neurologist at Children's Hospital in Boston, and an associate neuropathologist at Brigham and Women's Hospital. Id. at 3.

Dr. Lidov testified that C.L. fits the Triple Risk Model well—he was the right age, and had "some brainstem abnormalities and [] several of the recognized risk factors," and Dr. Lidov did not "see any particular reason to be searching for additional . . . new and novel risk factors." Tr. at 351-52. Dr. Lidov does not believe that the things that are accepted as risk factors exert their effect on SIDS through cytokines, and he is not aware that cytokines causally contribute to SIDS deaths. Id. at 339-40, 350. Dr. Lidov did not agree that vaccines, through a mechanism related to cytokines, should be accepted as a risk factor for SIDS. Id. at 337-38. He stated that doing so would be new and novel, and that he was "not aware of any review in papers or any of the relevant text of risk factors for SIDS which mention vaccines whatsoever." Id. at 337. According to Dr. Lidov, there is little or no epidemiological support for vaccines as a risk factor, and the things that *are* accepted as risk factors are accepted because they do have epidemiological support—not just because there is perhaps a plausible mechanistic reason. Id. at 338.

In his expert report, Dr. Lidov analyzed many of the articles cited by Dr. Miller and explained in detail the problems with Dr. Miller's conclusions.[35] He disagreed that the medical literature submitted by Dr. Miller supports the theory that cytokines associated with vaccination can play a causal role in SIDS. Resp. Ex. A at 6-8; Tr. at 351. Rather, he opined that "the role for inflammatory cytokines . . . does not bring a novel factor to light; it simply inserts a mechanistic step into the proposition that vaccines increase the risk of SIDS." Resp. Ex. A at 12. He agreed with Dr. McCusker that cytokines could be a response to a stressor, as opposed to a cause of the stressor. Tr. at 351.

Regarding the use of epidemiological studies in general, Dr. Lidov testified that "one gets as close a definitive answer from an epidemiologic study as one can get in medicine." Tr. at 349-50. He opined that if petitioners' theory were true, and vaccines were a sufficient exogenous stressor to cause SIDS in intrinsically vulnerable infants of the correct age, epidemiology studies should be able to pick it up. Id. at 348; Resp. Ex. A at 11.

e. Evaluation of the Evidence

Althen Prong One requires petitioners to set forth a reliable medical theory explaining how the received vaccines could have caused the alleged injury. Althen, 418 F.3d at 1278. While scientific certainty is not required to establish causation under the Vaccine Act (Id. at 1279), the theory must be supported by a "sound and reliable" medical or scientific explanation. Knudsen, 35 F.3d at 548.

i. Petitioners have failed to show that vaccines have been identified as an extrinsic risk factor under the Triple Risk Model

Petitioners have failed to show that their interpretation of the Triple Risk Model, as it relates to vaccines, is a sound and reliable medical theory. While petitioners' testimony and medical literature showed that the Triple Risk Model may be an accepted mechanism to explain some SIDS cases, they failed to show preponderant evidence that vaccines have been identified as an exogenous stressor implicated in the Triple Risk Model. Neither Dr. Miller nor Dr. Oleske produced evidence that others in the medical community support their opinion that vaccinations operate like infections as exogenous stressors for purposes of the Triple Risk Model of SIDS. Dr. Miller claimed that there is "abundant literature associating vaccinations with SIDS," but admitted that he was not sure anyone has "connected all those dots" between cytokines, cytokine production by vaccines, and vaccines specifically being a risk factor for SIDS in vulnerable infants. Tr. at 92, 96. The literature he cited reports cases of SIDS following vaccination, however, these studies and epidemiological studies do not identify vaccination as an exogenous risk factor. Upon review, there is little or no evidence presented to support petitioners' position, other than the testimony of Drs. Oleske and Miller. A special master does not need to credit "expert opinion testimony that is connected to the existing data or methodology 'only by the ipse dixit of the expert.'" Jarvis v. Sec'y of Health & Human Servs., 99 Fed. Cl. 47, 61 (2011) (quoting Cedillo ex rel. Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1339 (Fed. Cir. 2010).

[35] To review Dr. Lidov's complete analysis of the medical literature cited by Dr. Miller, see Dr. Lidov's expert report, Resp. Ex. A at 7-12.

ii. Petitioners have failed to show that URIs act as neurochemical risk factors, and that vaccines are comparable to infections as risk factors

Petitioners also failed to show by preponderant evidence that recognized extrinsic risk factors, and URIs in particular, act as neurochemical rather than mechanical risk factors. The evidence identifies URIs and gastrointestinal infections as risk factors for SIDS. Tr. at 184, 300-01. Dr. McCusker testified that the literature discussing "mild infection" as a risk factor generally refers to URI and GI infections—while a few point to something else, as other infections in infants are generally not considered "minor." Id. at 270. URIs and GI infections cause congestion or reflux, both of which affect an infant's breathing mechanics. Id. at 184. Dr. Miller opined that almost none of the extrinsic risk factors are "mechanical" risk factors, and that he was "not aware of any literature at all that supports the idea that there's a mechanical respiratory obstruction . . . in the sense of chest wall motion [being] restricted or anything like that, as a cause of SIDS in relation to . . . infections." Id. at 35-36, 99. Dr. Miller agreed, however, that prone sleeping was "an external reason that not enough oxygen is getting to the system." Id. at 99. Dr. McCusker testified that so-called "mechanical" risk factors are those that affect respiration by not only physically impeding the infant's ability to respire, but also by otherwise reducing oxygen intake. Id. at 184-85. For example, re-breathing exhaled air occurs when an infant is in the prone position. Id. at 183-84.

Dr. McCusker testified that there is no literature that supports the proposition that infections like mild upper respiratory infections are known to affect SIDS through the mediation of cytokines. Tr. at 202. Petitioners, on the other hand, cite the Rognum[36] and Kadhim[37] articles. Rognum found elevated levels of IL-6 in the brains of infants who died of CNS infection and SIDS compared to those who died of noninfectious sudden deaths. Tr. at 189; Pet. Ex. 36. Likewise, Kadhim found a difference in cytokine levels in the arcuate nucleus of SIDS victims versus non-SIDS victims. Pet. Ex. 34. However, as Dr. McCusker testified, these are "descriptive" studies demonstrating the presence of cytokines in the SIDS brain, and do not establish causation. Tr. at 189. Petitioners rely on these studies, and Dr. Miller agreed that the Rognum and Kadhim studies "only address the expression of cytokines, not the effect of cytokines." Id. at 100 (referencing Pet. Ex. 34, 36).

Dr. Miller also cited a review article of studies by Vege and Rognum[38] about the relationship between URIs and SIDS. The article noted "[s]everal observations of immune stimulation in the periphery and of Interleukin-6 elevation in the cerebrospinal fluid of SIDS victims explain how infections can play a role in precipitating these deaths." Tr. at 98 (citing Pet. Ex. 39 at 2). Dr. McCusker testified that this article was published in 2004, when the presence of IL-6 and IL-1β in the CNS was thought to be pro-inflammatory. Tr. at 183. At that time, it was known that increased IL-1 and IL-6 were found in the brains of SIDS infants, and the hypothesis was that an external trigger, such as slight infection, could lead to changes in cytokines that could lead to sudden death. Id. at 183-86. Now, however, the thinking is that the infections discussed as

[36] Pet. Ex. 36, Rognum, *supra* note 32.

[37] Pet. Ex. 34, Hazim Kadhim et al., *Distinct Cytokine Profile in SIDS Brain: A Common Denominator in a Multifactorial Syndrome?*, 61 NEUROLOGY 1256 (2003).

[38] Pet. Ex. 39, Ashild Vege & Torleiv Ole Rognum, *Sudden Infant Death Syndrome, Infection and Inflammatory Responses*, 42 FEMS IMMUN. & MED. MICROBIOL. 3 (2004).

risk factors for SIDS (URIs and GI infections), can both lead to mechanical obstruction, as discussed above. Id. at 184.

Petitioners argue that URIs are not the only infections that create a risk factor for SIDS, but rather that "mild infection and/or mild inflammatory process[es]" can also be external risk factors. Pet. Post-Hearing Brief at 26 (citing Pet. Ex. 37[39]). Petitioners' argument appears to hinge on the premise that vaccinations promote the production of pro-inflammatory cytokines in the same manner as a mild infection. The evidence does not support this premise. As Dr. McCusker testified, there are important similarities and differences between an immune response to an infection and an immune response to a vaccination. Importantly, cytokine production in response to a vaccination is localized and "do[es] not generate significant systemic signaling." Tr. at 157. The inflammatory response stays focused at the site of injection while the adjuvant exerts a depot effect, and it takes about 24 to 48 hours for the response to go from the thigh to the local lymph nodes, where it remains for about four days. Id. at 164-65. An infection, on the other hand, is a live organism that infects a cell directly and has the ability to replicate in the body and cause a significant immune reaction. Id. at 161-64. The vaccines C.L. received are composed of particulate killed organisms, i.e., pieces of organisms. Id. at 164. Administered alone, these particles do not elicit much of an immune response beyond a local reaction. Id. at 313. Adjuvants are added to vaccines to elicit a greater immune response to protect an individual who may later be exposed to the live virus. Id. at 164-65, 313.

iii. Petitioners have failed to show that vaccines cause a cytokine response that causes or contributes to SIDS in the manner their experts propose

The undersigned does not take issue with petitioners' argument that vaccinations result in a cytokine release and that some of these cytokines are the same ones released in response to infection. Petitioners have failed, however, to show that vaccines cause cytokines to produce an abnormal brainstem serotonin response or otherwise act in a manner that causes or contributes to SIDS, as their experts postulated. According to petitioners' theory, premised on the Triple Risk Model, a vulnerable infant encounters external stressor(s) during a critical time, resulting in death. Tr. at 17-20. In this model, an infant is vulnerable due to a defective serotonergic 5-HT system. See id. at 18-19. After reviewing slides of C.L.'s brain, the experts agree that C.L. had abnormalities in cells migrating from the rhombic lip, which is evidence that C.L. was a vulnerable infant within the Triple Risk Model. Id. at 24, 354. If an infant has a defective 5-HT system, the ability to arouse in hypoxic conditions will be compromised. Pet. Post-Hearing Brief at 21. Petitioners further theorize:

> If the increased cytokine production secondary to a mild infection or inflammatory process (such as vaccination) is superimposed on this vulnerable infant, her ability to respond or arouse is further compromised. In this regard, the evidence is clear that cytokines such as IL-1β have an inhibitory effect on 5-HT neurons, meaning that cytokine interaction with 5-HT neurons will decrease their firing and thereby dampen the arousal response.

[39] Pet. Ex. 37, Hazim Kadhim, et al., *Interleukin-2 as a Neuromodulator Possibly Implicated in the Physiopathoogy of Sudden Infant Death Syndrome*, 480 NEUROSCIENCE LETTERS 122 (2010).

Id. at 21-22 (citing Tr. at 33-34, 37-39; Pet. Ex. 35[40]; Resp. Ex. C-7[41]). The current understanding of the role of cytokines, however, as expressed by Dr. McCusker, is that cytokines act to signal the occurrence of a pathological process and do not themselves cause a pathologic event. Dr. McCusker explained how the understanding of the role of cytokine expression in the brain has changed over time. Petitioners' theory is premised on the idea that the cytokine expression in the SIDS brain causes inflammation and SIDS death in a vulnerable infant. While early studies showed that the pro-inflammatory cytokine, IL-1β, was present in the brains of SIDS infants, current research demonstrates that the brain regularly produces pro-inflammatory cytokines as part of a normal, regulatory process.

Petitioners have also failed to show that cytokine interaction with the 5-HT system necessarily operates to suppress arousal in a manner that would lead to a SIDS death. Dr. Miller asserted that while cytokines may be arousal molecules in general with regard to the sleep-wake cycle, not all arousal is the same. Tr. at 233-35. He said that the papers he presented show a suppression of 5-HT activity in the medullary 5-HT network, which is involved in stimulation, respiration and arousal from sleep during apnea or hypoxia. Id. Dr. McCusker, however, cited medical literature that indicates that cytokines improve, rather than impair, autoresuscitation in the context of sleep. Id. at 204-08. In particular, there is evidence in the papers regarding sleep that cytokines are involved in arousal. Id. at 298.

In support of the proposition that the 5-HT system is critical for recovery from apnea and that certain cytokines play a role in reducing recovery from apnea, Dr. Miller cited studies by Stoltenberg, Froen, and Brambilla.[42] Tr. at 70. In the Stoltenberg study, the CNS of newborn piglets was infused with IL-1β, and their environment was pumped full of ammonia, causing them to become hypoxic. Id. at 70, 209. When the environment was cleared, there was a delay in autoresuscitation in animals who had been filled with IL-1β. Id. In the Froen study, one-week old piglets were infused with IL-1β and nicotine, and it was found that the combination worsened apnea. Id. at 210. Brambilla looked at the effect of exposure to IL-1β of the firing on serotonin neurons and GABAergic neurons in the dorsal raphe nucleus of rats in the medulla, and found that it suppressed the firing of the serotonin neurons and increased the firing of the GABA neurons. Id. at 72.

Dr. McCusker critiqued these studies. First, Dr. McCusker testified that the effect seen by Stoltenberg is only observed in newborn piglets—possibly equivalent to a three week old human. Tr. at 210, 297. There is no evidence that IL-1β does harm after the neonatal period. Id. at 298. In

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[40] D. Brambilla et al., *Interleukin-1 Inhibits Firing of Serotonergic Neurons in the Dorsal Raphe Nucleus and Enhances GABAergic Inhibitory Post-Synaptic Potentials*, 26 EUR. J. OF NEUROSCIENCE 1862 (2007).

[41] Luca Imeri & Mark R. Opp, *How (and Why) the Immune System Makes Us Sleep*, 10 REVIEWS NEUROSCIENCE 199 (2009).

[42] Pet. Ex. 32, Lauritz Stoltenberg et al., *Changes in Apnea and Autoresuscitation in Piglets After Intravenous and Intrathecal Interleukin-1β Injection*, 22 J. PERINAT. MED. 421 (1994); Pet. Ex. 33, J. Frederik Froen et al., *Adverse Effects of Nicotine and Interleukin-1β on Autoresuscitation After Apnea in Piglets: Implications for Sudden Infant Death Syndrome*, 105 PEDIATRICS (2000); Pet. Ex. 35, D. Brambilla et al., *Interleukin-1 Inhibits Firing of Serotonergic Neurons in the Dorsal Raphe Nucleus and Enhances GABAergic Inhibitory Post-Synaptic Potentials*, 26 EUR. J. NEUROSCIENCE 1862 (2007).

addition, the quantity and location of cytokines administered to the piglets in the study is not akin to cytokines triggered by vaccination. Id. Second, in Brambilla, the researchers took the brains out of the rats, bathed them with IL-1β, and then stimulated them and observed changes in the firing. Id. One cannot necessarily infer that a decrease in firing means there will be a difference in function. The finding in animal studies has been that there is not a change in respiration post neonatal period. Id. at 298-99. Thus, Dr. McCusker did not agree that the studies showed that cytokines interface with the 5-HT neurons in the medulla and affect neurotransmission. Id. at 266. Dr. Lidov agreed, finding that the studies collectively have "limited applicability" to Dr. Miller's conclusions. See Resp. Ex. A at 7-9.

In discussing the articles cited by petitioners' experts regarding the role of cytokines, Dr. McCusker demonstrated that the information upon which petitioners' theory is based is outdated. Respondent's experts provided a detailed discussion on the current understanding of the role of cytokines. Petitioners' experts did little to dispute this current information. Until the role of cytokines is better understood through research, the question of whether cytokines act to cause pathology, as Drs. Oleske and Miller testified, or act to signal the occurrence of a pathological process, as Dr. McCusker testified, remains unanswered.

Petitioners have failed to demonstrate, by a preponderance of the evidence, that vaccinations are exogenous stressors under the Triple Risk Model of SIDS, or act similarly to other exogenous stressors that have been identified. Furthermore, even if petitioners were successful in providing evidence that vaccinations produce cytokine effects in the brain similar to infections, petitioners' theory still fails because they have not shown that the cytokines have a negative impact on the brain that would lead to SIDS death.

(2) Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, petitioners must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner[s] must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (citations omitted).

a. Petitioners' Expert, Dr. Miller

Dr. Miller testified that C.L. died of SIDS and that the vaccines were a substantial contributing factor to his death. Tr. at 10-11, 75. Dr. Miller testified that the peak incidence for SIDS is between two and three months of age, and that 90% of SIDS cases occur within the first six months of life. Id. at 29. Dr. Miller considered C.L. to have been five months old at the time of death, as he was born prematurely. Id. at 126. Thus, C.L.'s death occurred within the critical developmental period within the Triple Risk Model.

C.L. was a vulnerable infant, based on several facts. Tr. at 23. First, C.L. was premature, and therefore had "even less ability to respond . . . on top of whatever intrinsic vulnerability [he had due to his] developmental problem." Id. at 23, 27. Second, C.L. initially had hypothermia and desaturations when feeding, which were clinical signs of brainstem dysfunction. Id. at 23. In addition, C.L. was noted to have a dysconjugate gaze and failure to fixate at his two-month well-baby visit. Finally, based on his review of slides of C.L.'s brain, Dr. Miller agreed with Dr. Lidov

that the slides showed a group of cells that appeared to belong to the inferior olivary nucleus (part of the medulla) located out of place, more dorsally in the brainstem. See id. at 11-12, 344-46. Dr. Miller stated that the ectopic cells that should have been in the inferior olivary nucleus are "a fundamental indication of brainstem and specifically medullary development abnormality." Id. at 24.

Dr. Miller stated that "abnormality of the brainstem serotonin or the medullary serotonin network" and the brainstem abnormalities seen in C.L., in cells migrating from the rhombic lip to the medulla, have been described in SIDS cases as making an infant vulnerable. Tr. at 13-14, 22-23, 146. Dr. Miller testified that the abnormality points to an underlying developmental abnormality in C.L.'s brainstem. Id. at 145.

Recognized extrinsic risk factors, Dr. Miller testified, include things such as prone sleeping position, upper respiratory infection, or smoking in the house. Tr. at 30, 85. He opined that extrinsic risk factors act "synergistically" or at least in an additive fashion. Id. at 21, 138. As for sleeping position at the time of death, Dr. Miller believed that C.L. died supine, on his back. Id. at 84. C.L.'s grandmother found C.L. prone, face down. The medical examiner and the staff at the hospital observed posterior lividity. Id. at 83-84. Dr. Miller stated that he "tend[s] to trust lividity patterns more than [he] trust[s] eyewitnesses." Id. at 83. Dr. Miller conceded, however, that the medical examiner opined that the lividity pattern was "not inconsistent" with C.L. having died prone and then moved to his back after death. Id. at 84-85. Even if C.L. was in a prone position, Dr. Miller's opinion that vaccination played a causative role would not change. Id. at 138.

Dr. Miller agreed that gastroesophageal reflux is a risk factor for SIDS. Tr. at 85. However, he opined that the fluid found in C.L.'s mouth after death was more likely a response to death and resuscitation, rather than a cause of death. Id. at 75.

Dr. Miller opined that the evidence in this case indicated that peripherally produced cytokines communicated with C.L.'s central nervous system. Tr. at 36. C.L. exhibited sleepiness, tiredness, crankiness, fussiness, irritability, and decreased appetite following his vaccination, symptoms which Dr. Miller testified are consistent with cytokine effect on central nervous activity. Id. at 36-37, 79. The most classic evidence of peripherally produced cytokines communicating with the central nervous system is fever, which C.L. did not exhibit.

b. Petitioners' Expert, Dr. Oleske

Dr. Oleske opined that C.L. died of SIDS, and that the immunizations he received were the plausible cause of his SIDS death. Pet. Ex. 50 at 2. Dr. Oleske stated that infants with SIDS have latent defect(s) in the medullary serotonergic system, and that the "anatomical and epidemiological link to SIDS, when viewed in the temporal relationship of multiple vaccine administrations, supports a finding of a vulnerable subset of infants." Id. at 4-5. He opined that vaccines—like infections—should be considered an extrinsic risk factor in SIDS cases. Id. at 5. He stated that in the vulnerable infant, like C.L., experiencing extrinsic risk factors, cytokines may flood and accumulate in the extracellular compartment of tissues, impairing the cytokine network homeostasis, and contribute to local pathogenesis. Id. at 5-6. In the brain, the complex cytokine signaling "can occasionally be disrupted by an extrinsic factor such as a mild infection or, as in the case of [C.L.], the multiple vaccine antigens that he was immunized against…" Id. at 6. However, Dr. Oleske did not identify any specific factual support in the record for his theory that the vaccines

C.L. received triggered the release of cytokines. Rather, as support for his opinion that C.L.'s death was more likely than not related to his vaccinations, Dr. Oleske cited (1) the proximal temporal relationship of the multiple immunizations C.L. received and his SIDS death 48 hours later; (2) the "lack of any other plausible cause of death"; and (3) "significant evidence from investigations and understanding of the pathophysiologic interactions in the developing infant's brain suffering from SIDS." Id. at 6.

c. Respondent's Expert, Dr. McCusker

Dr. McCusker disagreed with petitioners' experts' conclusion that C.L.'s vaccinations played a contributing role in his death from SIDS. Supp. Expert Report of Dr. McCusker, Resp. Ex. E at 4. First, there was no evidence of cytokine activity in C.L.'s brain. Resp. Ex. C at 4. If C.L.'s vaccines had caused an increase of cytokines in his brain, "the resulting effect would most likely have been increased arousal and/or fever." Id. at 5. "The key cytokines activated in the first hours of an immune response, IL1B, IL6 and TNF-a, are implicated in the development of systemic symptoms such as fever and malaise. In the sleep/arousal centers of the brain these cytokines have distinct activities that, in part, increase rather than decrease arousal." Resp. Ex. E. at 3. C.L. had "no reported fever, the usual first clinical sign of systemic cytokine activity." Id. Further, although Dr. McCusker agreed that cytokines are associated with sickness behaviors, she testified that cytokines are not the only thing that can cause such behaviors. Tr. at 308.

Dr. McCusker opined that C.L. had several extrinsic risk factors that put him at risk for sudden infant death, and "there's no evidence that the vaccines were a component here." Tr. at 232. She testified that 99% of SIDS deaths have at least one risk factor for SIDS identified at the time of death, and 57% have two. Id. at 284 (citing Resp. Ex. C-11[43]). It "has been hypothesized that there may be synergy, but a single risk factor is sufficient." Id. at 284. Known extrinsic risk factors for SIDS include "prone or side sleeping, bed sharing, over-bundling, soft bedding" as well as smoking exposure and gastro-esophageal reflux. Pet. Ex. E at 2; Pet. Ex. C at 8.

Dr. McCusker believed that C.L. was found prone, based on his grandmother's statement. Tr. at 195. Dr. McCusker testified that prone sleeping position may affect breathing in two ways: first, by creating a pocket of rebreathable air (higher in carbon dioxide), and second, by mechanically preventing abdominal breathing. Id. at 194-95. Also, in C.L's case, there was evidence of milk in C.L.'s mouth and upper airway, and liquid in the crib consistent with reflux, as well as a history that he would spit up while he was on his tummy. Id. at 198. Gastro-esophageal reflux operates as a mechanical risk factor because it can induce the laryngeal chemoreflex—a reflex that induces transient apnea when there is food in the mouth (where the pharynx and esophagus meet). Id. at 196-97. Thus, Dr. McCusker concluded that the risk factors for SIDS present here included prone sleeping position, and the episodes of regurgitation. Resp. Ex. E at 3.

d. Respondent's Expert, Dr. Lidov

Dr. Lidov did not believe the vaccines were a substantial contributing factor to C.L.'s death. Tr. at 334. He believed that C.L. fit in the Triple Risk Model for SIDS without the need to

[43] Resp. Ex. C-11, Trachtenberg, *supra* note 8 at 630.

implicate vaccinations—C.L. was the right age, had brainstem abnormalities, and several recognized risk factors. Id. 351-52.

Dr. Lidov testified that "[m]aleness, prematurity, [and] being prone" are all risk factors for SIDS, as is gastro-esophageal reflux. Tr. at 344. Regarding the question of whether C.L. died in a prone position, Dr. Lidov testified that the most likely scenario was that C.L.'s grandmother found him in a prone position. The posterior lividity was caused by the child being turned over onto his back after death. Id. at 343-44, 355.[44] Dr. Lidov also opined that there was evidence that C.L. had refluxed, as the EMT report indicated there was "froth in the mouth and wetness on the sheets." Id. at 344.

Dr. Lidov testified that the abnormalities he observed in C.L.'s medulla indicated that there was a malformation in his brainstem, but do not necessarily indicate that there was specifically a defect in the neuronal circuits using serotonin as a neurotransmitter. Tr. at 346, 353. Nevertheless, Dr. Lidov opined that C.L.'s abnormality was an intrinsic brainstem abnormality contemplated in the Triple Risk Model. Id. at 346-47, 354.

e. Evaluation of the Evidence

Althen Prong Two requires preponderant evidence of a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Althen, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e., in petitioners' case, the question is whether the vaccine (or vaccines) caused the alleged injury. Broekelschen, 618 F.3d at 1345 ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case . . . ."); Pafford, 451 F.3d at 3. Temporal association alone is not evidence of causation. See Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992).

There is not preponderant evidence to support petitioners' theory that peripheral cytokines communicated with C.L.'s central nervous system in the pathological manner described by Dr. Miller and Dr. Oleske. Although Dr. McCusker agreed that there is communication between peripheral cytokines and the central nervous system, she did not agree that cytokines play a *pathological* role, but rather stated that cytokine expression in the brain is normal. In turn, petitioners' evidence described cytokine expression in the SIDS brain, but did not describe the effect of cytokines on the brain. Dr. Miller opined that crankiness, fussiness, irritability, and decreased appetite following his vaccination were indications that peripherally produced cytokines communicated with C.L.'s central nervous system. Tr. at 37, 79. However, the classic evidence of peripherally produced cytokines communicating with the central nervous system is fever, which C.L. did not exhibit. See Resp. Ex. E at 3. Even if the evidence were sufficient to support a finding that peripheral cytokines communicated with C.L.'s nervous, system, there is no evidence to suggest that the communication was causally connected to C.L.'s death.

[44] In his written expert report, Dr. Lidov stated that he believed the pattern of lividity indicated C.L. died supine, contrary to the grandmother's account. Resp. Ex. A at 3. However, at the hearing, he testified that his opinion changed once he understood the short time interval between C.L.'s death and when he was turned over to the prone position. See Tr. at 343.

In addition, as Dr. Lidov explained, C.L. met the criteria for the Triple Risk Model of SIDS without the need to consider a speculative risk factor. Tr. at 351-52. C.L. died during the first six months of life and had brainstem abnormalities of the type described in the Triple Risk Model. He had several known intrinsic risk factors for SIDS, including the fact that he was premature and male. Id. at 288, 323-24. In addition, there is evidence C.L. experienced gastro-esophageal reflux, an extrinsic risk factor for SIDS. Id. at 344. Finally, there is preponderant evidence that C.L. was found in the prone position—C.L.'s grandmother reported finding C.L. prone, and Dr. Lidov agreed that this was the most likely scenario. Id. at 342-43. All experts agree that being prone is a significant risk factor for SIDS.

For these reasons, the undersigned finds that petitioners failed to provide preponderant evidence of a logical sequence of cause and effect showing that C.L.'s vaccinations caused his death.

(3) Althen Prong Three: Proximate Temporal Relationship

Under Althen Prong Three, petitioners must provide "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." De Bazan, 539 F.3d at 1352. The acceptable temporal association will vary according to the particular medical theory advanced in the case. See Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 356 (2011) (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting the vaccine and injury").

a. Petitioners' Expert, Dr. Miller

Dr. Miller testified that C.L. received his vaccinations, exhibited abnormal behavior over the following day and a half to two days, and then died within 48 hours of immunization. Tr. at 8-9, 28. He testified that in the literature that describes a temporal association between vaccination and SIDS, the majority of cases have occurred in a window of out to four days post-vaccination, with the peak being about 48 hours after vaccination. Id. at 28-29; see also, Pet. Ex. 22 at 7 (citing Pet. Exs. 41, 43, 45[45]).

b. Petitioners' Expert, Dr. Oleske

Dr. Oleske noted that C.L. died about 48 hours after receiving his vaccinations. Pet. Ex. 50 at 2. Dr. Oleske concluded that the proximal temporal relationship of the multiple immunizations and C.L.'s SIDS death, along with the lack of other plausible causes of death and evidence from the understanding of the pathophysiological interactions in the SIDS brain make C.L.'s death more likely than not related to the vaccines he received. Id. at 6.

[45] Pet. Ex. 41, B. Zinka et al., *Unexplained Cases of Sudden Infant Death Shortly After Hexavalent Vaccination*, 24 VACCINE 5779 (2005); Pet. Ex. 43, Giuseppe Traversa et al., *Sudden Unexpected Deaths and Vaccinations During the First Two Years of Life in Italy: A Case Series Study*, PLOS ONE 2011; 6E 16363 (2011). As Dr. Lidov notes in his report, the citation to exhibit 45 appears to be a typographical error, as it is a study of *H. pylori* in mice.

c. Respondent's Expert, Dr. McCusker

Dr. McCusker explained the sequence of events that occurs after vaccination. When a vaccine is administered, the inflammatory response stays focused at the site of injection while the adjuvant exerts a depot effect. Tr. at 164-65. It takes about 24 to 48 hours for the response to go from the thigh to the local lymph nodes, where it remains for about four days. Id. at 165.

The "key cytokines active during the first hours of an immune response, IL1B, IL6 and TNF-a, are implicated in the development of systemic symptoms such as fever and malaise." Resp. Ex. E at 3. Thus, "[f]ever as a sign of systemic cytokine activity may [] occur after several hours," and would generally develop within the first day after receiving a vaccination—from six to twelve hours after—and is usually gone by 24 to 48 hours. Id.; Tr. at 265-66. Dr. McCusker noted that C.L. "had no reported fever, the usual first clinical sign of systemic cytokine activity." Resp. Ex. E at 3.

d. Respondent's Expert, Dr. Lidov

Dr. Lidov stated that the references cited by Dr. Miller in support of the statement that there is an elevated risk for SIDS within the first 48 hours following immunization do not represent a statistically significant number of cases. See Resp. Ex. A at 10.

e. Evaluation of the Evidence

In the present case, there is a temporal relationship between C.L.'s vaccination and his death. However, a temporal relationship alone cannot establish causation, nor is it sufficient on its own to meet Althen Prong Three. Veryzer, 100 Fed. Cl. at 356. Rather, there must be "preponderant proof that the onset of symptoms occurred within a timeframe for which, *given the understanding of the disorder's etiology,* it is *medically acceptable to infer causation-in-fact.*" De Bazan, 539 F.3d at 1352 (emphasis added). Under Althen Prong Three, petitioners must establish the timeframe for which it is medically acceptable to infer causation, assuming C.L.'s death was caused by the vaccination, and they must show that C.L.'s death occurred in that timeframe. See Shapiro v. Sec'y of Health & Human Servs., 105 Fed. Cl. 353 (Fed. Cl. 2012). Petitioners' experts offered evidence that death 48 hours after vaccination is consistent with the timing of death in studies reporting an association between death and vaccination. Thus, petitioners have met their burden under Althen Prong Three.

A temporal relationship between C.L.'s vaccination and his death alone, however, is insufficient to establish causation. Petitioners failed to provide preponderant evidence of a reliable medical theory and a logical sequence of cause and effect under Althen Prongs One and Two, respectively. A temporal relationship alone is not sufficient to establish causation in fact without preponderant evidence of the two remaining factors. See Veryzer, 98 Fed. Cl. at 227 (citing Grant, 956 F.2d at 1148). Thus, petitioners' failure to meet Althen Prongs One and Two means that they cannot be compensated. See, e.g. Koehn v. Sec'y of Health & Human Servs., 2013 WL 3214877 (Fed. Cl. Spec. MsTr. at May 30, 2013) (citing Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1364-65 (Fed. Cir. 2012) (holding the special master did not err in resolving the case pursuant to Prong Two when respondent conceded that petitioner met Prong Three).

V. CONCLUSION

For all of the reasons discussed above, the undersigned finds that petitioners have not established entitlement to compensation and their petition must be dismissed. In the absence of a timely filed motion for review filed pursuant to Vaccine Rule 23, the clerk is directed to enter judgment consistent with this decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Chief Special Master